DOI:
10.2337/dc16-2331

Document Version
Peer reviewed version

Excess body mass index in childhood: a modifiable risk factor for type 1 diabetes development?

Excess BMI and risk for type 1 diabetes in childhood

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Objective: The rising incidence of type 1 diabetes parallels an increased prevalence of obesity, yet the causal association remains inconclusive. Analyses often examine BMI at a single time point without emphasis on duration of BMI elevation. We aimed to determine the cumulative effect of elevated BMI over time on the progression to type 1 diabetes in youth, and to study the impact of age and sex on this relationship.
Research Design and Methods: We studied 1,117 pediatric participants in the TrialNet Pathway to Prevention cohort, i.e. autoantibody-positive relatives of patients with type 1 diabetes. Longitudinally accumulated BMI above the 85th age- and sex-adjusted percentile was calculated to generate a cumulative excess BMI (ceBMI) for each subject. Recursive partitioning analysis and multivariate modeling yielded sex and age-specific thresholds for ceBMI that confer the greatest risk for type 1 diabetes progression.
Results: ceBMI ranged from -10 to +15.1 kg/m^2 (median -1.86), with 0 corresponding to the CDC definition of elevated BMI ($\geq$85th BMI percentile). Higher ceBMI corresponded to significantly greater risk of progressing to type 1 diabetes (p=0.0006). The increased risk of diabetes occurred at lower ceBMI values in children <12 years compared to older subjects, and in females versus males.
Conclusions: Elevated BMI is associated with increased risk of diabetes progression in pediatric autoantibody positive relatives, but the effect varies by sex and age. These data suggest that lifestyle modifications to lower BMI may delay the onset of type 1 diabetes and offers specific BMI thresholds for implementing these changes.

The global rise in incidence of type 1 diabetes has intensified efforts to identify modifiable risk factors in order to prevent or delay onset of clinical diabetes(1; 2). Although there are several genetic loci for type 1 diabetes susceptibility, heritability does not completely predict disease development, highlighting the role of other factors such as environmental influences(3). The parallel rise in obesity (4; 5) and type 1 diabetes incidence suggests a potential link between elevated body weight and type 1 diabetes progression(6-9). The “accelerator hypothesis” proposes that obesity-induced insulin resistance exacerbates the autoimmune-mediated beta cell destruction that characterizes type 1 diabetes (10). Obesity-induced insulin resistance may also accelerate clinical onset of type 1 diabetes by increasing insulin needs in those with already compromised insulin secretory capacity(11).

Data from the Diabetes Prevention Trial (DPT-1) indicate that insulin resistance is an independent risk factor for type 1 diabetes development(12). Moreover, the Diabetes Prevention Trial-Type 1 Risk Score (DPTRS), a predictive tool of diabetes progression in the DPT-1 at-risk population, incorporates BMI as a critical component(13). More recently, however, BMI percentile was found to be only a minor risk factor for diabetes progression in antibody positive relatives of people with type 1 diabetes participating in the TrialNet Pathway to Prevention (PTP) cohort(14), although this study included both children and adults. Other prospective(15-17) and cross-sectional(11; 18; 19) studies report conflicting data for the role for body weight and obesity on type 1 diabetes progression, further highlighting the controversial nature of the accelerator hypothesis. The majority of prospective observational studies, however, limit their analysis to BMI at a single time point prior to disease diagnosis, and the impact of sustained BMI elevation measured longitudinally over time on risk of progression to type 1 diabetes remains unknown. In addition, the influence of sex and age on the relationship of BMI and progression to type 1 diabetes has yet to be explored.

Our overall objective was to determine the effect of sustained BMI elevation over time on the progression to type 1 diabetes in children at risk, and to study the impact of age and sex on this relationship. Here, we evaluated the longitudinal influence of cumulative excess BMI (ceBMI), a calculated aggregate measure of elevated BMI over time, on progression to type 1 diabetes in children participating in the TrialNet PTP cohort. Our evaluation focusing on the pediatric subjects of the PTP cohort allowed for unique investigation into sex- and age- specific influences on ceBMI and risk of type 1 diabetes progression.

Research Design and Methods:

Subjects: The TrialNet PTP cohort was established in 2001 and has been described previously(20). Briefly, nondiabetic first-degree relatives (ages 1–45 years) and second- or third- degree relatives (ages 1–20 years) of individuals with type 1 diabetes were enrolled and screened for presence of pancreatic islet antibodies. Antibody status was assessed according to the Diabetes Antibody Standardization Program(21). Participants were tested first for the presence of glutamic acid decarboxylase 65 (GAD65), insulin (IAA), or islet-antigen 2 (IA-2/ICA512) antibodies, and if positive, they were tested for islet cell antibodies (ICA) antibodies(22). Measurement of zinc transporter 8 (ZnT8) antibodies was initiated in 2004(23), and was consistently measured in the PTP cohort

starting in 2012. Confirmed autoantibody positive individuals were observed longitudinally with either semi-annual or annual monitoring, which included measurement of height and weight, and oral glucose tolerance testing (OGTT)(24).

A total of 3,285 eligible individuals were screened from March 2004 through June 2014, and were monitored for progression to diabetes through November 2015. To facilitate consistent and valid calculations of BMI percentiles and use of CDC criteria and guidelines to define overweight and obesity, we restricted our analysis cohort to only include participants age 2 to 18 years at their first BMI evaluation and who had at least two BMI measurements at monitoring visits before 20 years of age. Our resulting cohort consisted of a total of 1,117 subjects (Figure S1). One subject with severe morbid obesity and no other known conditions was excluded from final analysis to prevent limitation of generalizability of the results. All analyses were run with and without this subject to ensure that exclusion did not introduce bias, but data presented are without this subject. Baseline assessment for metabolic and anthropometric measurements is defined as the first visit with a BMI evaluation. Participants who later entered prevention trials were censored at the time of initial enrolment into the prevention trial.

Laboratory and anthropometric measurements: At each study visit, a standard protocol OGTT was performed and HbA1c was obtained. Glucose was measured using the glucose oxidase method(25). Diabetes was diagnosed according to American Diabetes Association criteria (fasting glucose ≥126mg/dl, random glucose ≥200mg/dl, 2 hour OGTT $\geq$200 mg/dl)(26), which must have been met on two occasions. A HbA1C $\geq$6.5% could be used as part of confirmatory testing(20).

BMI was calculated as weight (kg)/height(m^2). The CDC 2000 growth charts (www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm) were used to obtain the value for 85th percentile for age- and sex- adjusted BMI for each subject at the time of each study visit. Cumulative excess BMI, hereby referred to as ceBMI, has been used previously as a measure of persistent elevation of BMI beyond the overweight threshold(27; 28). The weighted sums of the differences between the actual BMI and corresponding 85th BMI percentile for the sex and age at that evaluation were calculated using the method described by Lee et al (27) and Bouchard et al (28). Briefly, a ceBMI score was calculated by summing the difference calculated at each BMI assessment while accounting for the irregular timing between evaluations (equation 1):

$$ceBMIyrs_j = \sum_{i=0}^{m} \frac{\left(BMI_{t_i} - 85^{th} percentile\ BMI_{t_i}\right) + \left(BMI_{t_{i+1}} - 85^{th} percentile\ BMI_{t_{i+1}}\right)}{2} x \left(\frac{number\ of\ days\ between\ t_i\ and\ t_{i+1}}{365.25}\right) \quad (1)$$

where $ceBMIyrs_j$ = ceBMI-years for subject j in units kg/m^2*years, and m = the number of BMI evaluations for subject j. We further annualized ceBMIyrs to accommodate the irregular timing of BMI assessment in relation to time type 1 diabetes outcome or censoring in some subjects of our cohort (equation 2).

$$ceBMIj = \frac{ceBMI_{yrsj}}{\frac{t_m - t_0}{365.25}} \quad (2)$$

where $ceBMI_j$ is a value representing the annual average ceBMI in kg/m^2 for subject *j* over the number of years subject j had m BMI evaluations, t_m is time in days at the last BMI measurement, and t_0 is the time of first BMI evaluation.

To avoid confounding by weight loss that frequently precedes diagnosis of type 1 diabetes, for individuals who progressed to diabetes, the last BMI used was $\geq$6 months prior to the date of diagnosis

Statistical Considerations: Categorical variables were compared among groups by Pearson's X^2 tests or Fisher Exact tests when cell sizes were insufficient. The majority of continuous variables summarized had skewed distributions and were compared between groups using nonparametric tests (Wilcoxon rank sum tests or Kruskal-Wallis tests, depending on the number of groups). Nonparametric Spearman rank correlation tests were used to assess correlation between continuous measures at baseline. Analyses of BMI were based on age- and sex-adjusted BMI percentiles. As such, baseline underweight status was defined as less than the 5th percentile, normal weight between the 5th and 85th percentile, overweight status at the 85th percentile or above, and obesity at the 95th percentile or above. Cumulative excess BMI was analyzed both as continuous measure as well as a dichotomized measure. Cumulative excess BMI $\geq$0 indicated a subject's BMI on average greater than or equal to the 85th percentile for their sex and age during the observation period.

The main clinical outcome for analysis was time to development of type 1 diabetes, defined as the time from the first BMI evaluation to the date of diagnosis. Those not diagnosed with type 1 diabetes were censored at their last date of follow up. In addition, those who during the course of their follow up enrolled in an interventional trial for the prevention of type 1 diabetes were censored on the date of their enrollment. Kaplan-Meier methods were used to assess differences in the time to type 1 diabetes distributions between groups of interest, and Cox proportional hazards models were used to assess the influence and significance of continuous and categorical variables. Assumptions for proportionality of hazards were tested for in these models. Given the known existence of risk factors and their potentially confounding effects, all time-to-event analyses were adjusted for age, sex, and whether or not subjects were single confirmed autoantibody positive versus multiple autoantibody positive at screening. To assess possible cut-points for ceBMI and age at first BMI evaluation in terms of their influence and stratification of risk on time to type 1 diabetes, we utilized recursive partitioning analyses(29) (rpart package in R). A model-based and iterative approach, specifically recursive partitioning analyses, was used to identify the "optimal" cut-point of the marker that best discriminated the outcome of interest, i.e. time to progression to type 1 diabetes.

We further evaluated each of the multivariable models with additional adjustment for high-risk HLA status (i.e. carrying the highest risk HLA DR3-DQ2/DR4-DQ8 genotype). HLA data were only available for a portion of the subjects and thus the main results presented without this adjustment. However, as a sensitivity analysis restricted to those with HLA data, we assessed the retention of results, both in terms of significance and impact when adjusted for HLA.

Overall, inferential tests were two-sided, with p-values <0.05 considered to be statistically significant. For interaction terms, p-values <0.1 were considered sufficient

for further exploration and evaluation of relationships given the sample size and number of events. All analyses were conducted in the statistical program R (version 3.1.2 for Windows).

Results

Demographics: A total of 1,117 pediatric subjects between the ages of 2 and 18 years at the first BMI evaluation from the TrialNet PTP study were included in these analyses (Table 1). Of these, 220 subjects (20%) developed diabetes during the observation time. The median age at the first visit with BMI data available was 10.1 years (IQR: 6.7 to 13.3), and the median BMI percentile at their first evaluation was 63.8%(IQR: 36.6 to 84.8). Fourteen percent of individuals were overweight (BMI $\geq$85th-<95th percentile) and 11% were obese ($\geq$95th percentile).

There was a spectrum of ceBMI from -10 kg/m^2 to +15.1 kg/m^2 (median ceBMI -1.86 kg/m^2; IQR: -3.6 to -0.03 m^2/kg). Nearly 25% of subjects (273/1117) had ceBMI values $\geq$0 kg/m^2 representing sustained excess BMI above the CDC threshold defining elevated BMI (overweight or obesity). There were no significant differences in age at first visit between those who were persistently overweight or obese compared to those of normal ceBMI (median ages 10.2 vs. 10.1 years, respectively, p=0.10). Similarly, no significant differences in distribution of males to females based on ceBMI $\geq$0 kg/m^2 versus <0 kg/m^2 (p=0.67). Further, the continuous measure of ceBMI was not significantly different between males and females (p=0.54).

Cumulative excess BMI influences progression to type 1 diabetes. In this pediatric cohort, we found that higher ceBMI was associated with significantly greater risk of progression to type 1 diabetes, which persisted after adjusting for age at first BMI evaluation, single versus multiple autoantibody status, and sex. For each 1 kg/m^2 increase in ceBMI, there was a 6.3% increased relative risk of type 1 diabetes progression (HR=1.063, 95% CI 1.03- 1.10, p=0.0006) (Table 2).

To evaluate the influence of having an elevated BMI compared to remaining normal weight over time, ceBMI was dichotomized at the threshold for overweight status for sex and age (ceBMI $\geq$0 kg/m^2 vs. <0 kg/m^2). Again we found that individuals who on average were persistently overweight or obese during the observation time had significantly greater risk of progressing to type 1 diabetes than those who on average kept below the 85th percentile for BMI, even after adjusting for age, sex, and single versus multiple antibody (HR=1.63, 95% CI: 1.22-2.18, p=0.0009, Table 2).

Age- and sex-specific ceBMI diabetes risk thresholds

Age at baseline was a significant independent risk factor for type 1 diabetes progression (HR=0.94, p=0.0006), adjusted for ceBMI, sex, and antibody status. Interestingly, there was an interaction between age and sex together with ceBMI in relation to time to diabetes that achieved significance necessary to investigate age and sex specific strata(p=0.072). Using recursive partitioning algorithms, we first identified the age cut-point defining greatest risk for type 1 diabetes progression. In both the combined cohort and in females alone, the cut-point for age that best differentiated subjects in terms of risk of progression to type 1 diabetes was just below 12 years at first BMI evaluation (all: 11.68 years; F: 11.77 years). In males, the optimal age cut-

point was similarly just under 12 years old (11.68 years) for subjects not in extremes of the ceBMI range (i.e. ceBMI -5.4 and 6.1). Furthermore, within each age group of <12 and ≥12 years, age was no longer a significant factor for males or females (p-value range 0.34-0.80). Therefore, it was determined that the influence of age on time to type 1 diabetes was well captured by this cut-point, and age dichotomized as ≥12 versus <12 years old at first BMI was used for subsequent analyses.

We again used recursive partitioning analysis as well as multivariable model-based diagnostics to identify cut-points for ceBMI that best differentiate risk for progression to diabetes, hereafter referred to as "ceBMI diabetes risk threshold". We found that age modified the effect of ceBMI on diabetes risk. The ceBMI diabetes risk threshold was lower in children younger than 12 years of age than in individuals over 12 years of age, regardless of sex (ceBMI diabetes risk threshold of -1.4 kg/m^2 for <12 years old, vs. ceBMI diabetes risk threshold of 4.6 kg/m^2 for ≥12yo, Table 3). That is, the increase in type 1 diabetes risk occurs at lower levels of sustained excess BMI in younger than older children. On the contrary, older children needed to have a sustained excess BMI that was well over the overweight/obese threshold to significantly increase their risk of progression to diabetes.

We did observe an interaction between sex and ceBMI as a continuous variable (p=0.087), leading to an investigation of sex-specific ceBMI diabetes risk thresholds (Figure 1, Table 3). Males overall had a higher ceBMI diabetes risk threshold to increase risk of type 1 diabetes than females, suggesting an increased sensitivity to BMI in female subjects. Within age subsets, males who were ≥12 years at the time of their first BMI evaluation were detrimentally affected by excess body mass at a ceBMI diabetes risk threshold of 5 kg/m^2 (Figure 1B), much higher than the ceBMI defining an overweight/obese state (Figure 1A). Similarly, in males who were <12 years old at their first BMI evaluation, a ceBMI diabetes risk threshold of 2.5 kg/m^2 (Figure 1D), again above the overweight threshold (Figure 1C), best differentiated risk of type 1 diabetes. In contrast, females who were ≥12 years old at their first BMI evaluation had a ceBMI diabetes risk threshold of 0 kg/m^2 that differentiated their risk (Figure 1F), consistent with the CDC definition of overweight/obese status (Figure 1E). Females <12 years old at their first evaluation had a lower ceBMI diabetes risk threshold compared to males of the same age, with a ceBMI diabetes risk threshold of -1.35 kg/m^2 (Figure 1H) suggesting that BMI percentiles below the overweight/obese threshold (Figure 1G) still increase type 1 diabetes risk in this subgroup.

Additional adjustment for the presence of the highest risk HLA genotype, i.e. DR3-DQ2/DR4-DQ8, demonstrated that age- and sex- group specific cutoffs were still significant within the models, and hazard ratios were consistent with models without this adjustment.

Conclusion

The increasing incidence of type 1 diabetes over the last several decades underscores the urgent need to identify risk factors for disease progression(1; 2). Obesity is a known risk factor for type 2 diabetes, and the concept that obesity also accelerates progression to type 1 diabetes has gained interest(10; 30). Our data indicate that ceBMI, i.e. sustained elevation of BMI, is an important risk factor for type 1 diabetes progression, but that the effect varies by sex and age. In our cohort,

partitioning analyses identified an age cutoff of 12 years that stratified the effects of sustained elevation of BMI on risk of type 1 diabetes progression, and was used to define group-specific ceBMI diabetes risk thresholds. Older age diluted the effect of elevated BMI as demonstrated by the increased risk of type 1 diabetes in individuals <12 years of age at a ceBMI diabetes risk threshold of -1.4 kg/m^2, lower than the ceBMI diabetes risk threshold of 4.6 kg/m^2 in subjects older than 12 years of age (Table 3).

This age-dependent effect of sustained excess BMI on type 1 diabetes progression is present in both male and female sex strata, but ceBMI diabetes risk thresholds are additionally modified by sex (Table 3, Figure 1). Male subjects had higher ceBMI diabetes risk threshold defining increased risk for diabetes progression than females of the same age. A more severe degree of ceBMI (i.e. ceBMI diabetes risk threshold $\geq$5 kg/m^2) determined increased risk of type 1 diabetes in males $\geq$12 years old, where in females $\geq$12 years old, any elevation above a ceBMI 0 kg/m^2 (defining overweight or obese according to the CDC 85th percentile) enhanced risk. Similarly, in younger subjects <12 years of age, males required a higher ceBMI to increase risk of type 1 diabetes compared to females (ceBMI diabetes risk threshold $\geq$ 2.5 kg/m^2 vs. ceBMI diabetes risk threshold $\geq$ -1.35 kg/m^2, respectively). Therefore, our data suggest that the detrimental effect of elevated BMI on progression to diabetes occurs at a lower BMI in girls than in boys, and BMI values below the threshold defining overweight can adversely affect progression to diabetes in girls under age 12 years old.

Past studies of the effects of BMI on type 1 diabetes have not yielded consistent results. In a case-control investigation, Kuchlubaer et al found that while birth weight was a risk factor for type 1 diabetes, BMI measured 5 years before diagnosis did not impact the age of disease onset(18). A study of the population participating in the SEARCH study demonstrated an association with earlier age of type 1 diabetes onset with higher BMI at diagnosis, but this was only seen in patients with lower fasting C-peptide levels indicative of baseline compromised beta-cell function(11). The Pittsburgh cross-sectional study similarly found no relationship between BMI at the time of type 1 diabetes diagnosis and age of disease onset(19)

Prospective studies of at-risk individuals have also failed to show a consistent impact of BMI on type 1 diabetes. The US Diabetes Autoimmunity Study in the Young (DAISY) found no association of progression to diabetes with BMI or weight(16). A study of the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) Study found that BMI standard deviation was a main independent predictor for diabetes, however after excluding obese subjects, this was no longer the case(17). A recent exploration of The Environmental Determinants of Diabetes in the Young (TEDDY) Study reported weight Z-score to be a risk factor for antibody seroconversion, but failed to show an effect on type 1 diabetes progression(15). Other prospective cohort studies of antibody-positive at risk subjects indicate that baseline insulin resistance, as assessed by HOMA, may increase risk of type 1 diabetes (8; 12; 31; 32). In fact, BMI at enrollment was found to be an independent risk factor for type 1 diabetes progression in DPT-1 participants, and is a component of the diabetes risk score which has been validated in other cohorts(13). However, a study of the both adult and pediatric participants of the TrialNet PTP cohort demonstrates only a minor effect of increased baseline BMI percentile on risk to disease progression, and no influence on antibody seroconversion(14).

Many of these prior prospective studies limited analyses to one measurement of BMI (e.g. birth weight, weight at cohort enrollment) without considering the interval values. Childhood is a dynamic time of rapid growth and pubertal development, and our analysis restricted to pediatric participants of the PTP permitted unique exploration of this time period. Growth hormone and sex hormones are not only known to alter insulin secretion and sensitivity, but are in turn altered by adipose tissue (33; 34). Our evaluation of ceBMI on type 1 diabetes progression uses an aggregate measure of elevated BMI over time among pediatric subjects in the PTP at risk cohort, thus taking advantage of longitudinal data. This model has been used in previous studies assessing persistent obesity on type 2 diabetes incidence and was demonstrated to be more accurate than using a single BMI measurement(27; 28). Our study is the first to apply this methodology to type 1 diabetes and revealed that ceBMI increased the risk of type 1 diabetes (HR=1.063, p=0.0006, Table 2). Beyond incorporation of longitudinal data, ceBMI measurement offers the additional advantage of an unrestricted upper limit compared to BMI percentile, and may offer greater resolution than a standard deviation or BMI Z-score.

A potential explanation for the differential effect of ceBMI on type 1 diabetes risk by sex, i.e.: different ceBMI diabetes risk thresholds, could be related to the discrepant correlation between BMI and adiposity in males and females(35; 36). This divergence may be more apparent during puberty as studies show that the correlation between BMI and percent body fat is nonlinear during this time, especially in non-obese individuals(37; 38). Lean body accrual in puberty is more apparent in males, further skewing the relationship of BMI to percent body fat compared to females. This is demonstrated by an increase in percentage body fat with each pubertal stage in females, yet in males the early peak in body fat is followed by a decline between Tanner stages 2-3(39). Our data reveal age- and sex-specific ceBMI diabetes risk thresholds, consistent with published literature where BMI captures adiposity and obesity differentially in males versus females throughout development. More sensitive anthropometric measures such as percent body fat or waist circumference (40) may be needed to supplement BMI measurements in deciphering sex-specific risk of obesity on type 1 diabetes.

The overall objective was to determine whether persistently elevated BMI is associated with progression to type 1 diabetes, rather than to determine whether fluctuations in BMI increase risk. While this study shows that sustained BMI excess is a type 1 diabetes risk factor, it cannot specifically address the effects of acute changes in BMI on disease onset. We did assess the intra-subject variability of BMI percentiles as well as the differences in visit-specific BMI excess above sex- and age-adjusted overweight/obese reference BMIs. A large majority of subjects (84%) remained classified as persistently above the overweight/obese threshold or persistently below this level for all BMI evaluations included in this analysis.

Our data suggest that puberty plays a significant role in defining ceBMI diabetes risk thresholds for type 1 diabetes progression. Limitations of this study include the lack of Tanner staging and sex hormone measurements which could elucidate mechanism of the identified age- and sex-specific ceBMI diabetes risk thresholds. An additional limitation of the dataset is a small number of diabetes events in some age and sex strata that may affect the precision of our estimates. Finally, it should be noted that our

study investigated an at-risk cohort of autoantibody-positive relatives of subjects of type 1 diabetes, and while heterogeneous, may not be broadly generalizable to the general population.

In summary, our results indicate that sustained elevation of BMI accelerates progression to type 1 diabetes in an at-risk pediatric population. Moreover, we demonstrate that CDC BMI cut-points at the 85th percentile may not appropriately define "excess BMI" in all pediatric subjects as it relates to type 1 diabetes development. Obesity is postulated to hasten progression to type 1 diabetes either by accelerated beta-cell loss or through mismatched insulin production and insulin demand. Future analysis to characterize the mechanisms underlying the effect of elevated BMI on type 1 diabetes risk, and the influence of age and sex are warranted. Our data imply that lifestyle and behavioral modifications may delay onset of disease, and importantly suggests age- and sex-specific ceBMI diabetes risk thresholds in which to implement such changes.

Acknowledgements

Funding: The sponsor of the trial was the Type 1 Diabetes TrialNet Pathway to Prevention Study Group. Type 1 Diabetes TrialNet Pathway to Prevention Study Group is a clinical trials network funded by the National Institutes of Health (NIH) through the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Allergy and Infectious Diseases, and The Eunice Kennedy Shriver National Institute of Child Health and Human Development, through the cooperative agreements U01 DK061010, U01 DK061034, U01 DK061042, U01 DK061058, U01 DK085465, U01 DK085453, U01 DK085461, U01 DK085463, U01 DK085466, U01 DK085499, U01 DK085504, U01 DK085505, U01 DK085509, U01 DK103180, U01-DK103153, U01-DK085476, U01-DK103266 and the Juvenile Diabetes Research Foundation International (JDRF). This work was also partially supported by the NIH grant K12-DK-094726 (C.T.F.) and U01-DK-103180-01 (M.J.R.). The contents of this Article are solely the responsibility of the authors and do not necessarily represent the official views of the NIH or the JDRF.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Author Contributions. All authors are members of the Type 1 Diabetes TrialNet Study Group.
Author contributions: C.T.F. designed the analysis and study design, researched data and wrote the manuscript. S.M.G. analyzed the data and contributed statistical support and writing of the manuscript. C.E.M., Y.F.L., R.B., I.M.L., D.J.B., H.R., A.M. and S.E.G. reviewed and edited the manuscript, and contributed to discussion. M.J.R. contributed to data analysis design, interpretation of results and critically revised the manuscript. M.J.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Prior Presentation: This work was presented at the 76th Scientific Sessions of the American Diabetes Association, New Orleans, June 2016. It was also the recipient of the Modan Memorial Award.

Figure Legends

Figure 1. Age and sex-specific ceBMI diabetes risk thresholds compared to traditional overweight/obese thresholds. Proportion type 1 diabetes free among pediatric subjects of the PTP cohort, comparing overweight/obese threshold, i.e. ceBMI ≥0 (based on 85th percentile for age and sex-adjusted BMI) (left panels) versus ceBMI diabetes risk thresholds identified by recursive partitioning algorithms (right panels). Male ≥12 years (A-B), male <12 years (C-D), females ≥12 years (E-F), females <12 years (G-H). All models adjusted for antibody number (single versus multiple).

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Table 1. Demographics and baseline characteristics of PTP subjects.

Characteristic	Overall cohort (n=1117)	Females (n=534)	Males (n=583)	p value*
Age at 1st BMI evaluation (years)				
Median (IQR)	10.1 (6.7; 13.3)	9.6 (6.4; 13.3)	10.5 (7.1; 13.2)	0.24
Range	2.0 to 17.96	2.0 to 17.94	2.0 to 17.96	
Progressed to type 1 diabetes				
No	897	437	460	
Yes	220	97	123	
# of BMI evaluations/subject				
Median (IQR)	4 (3; 6)	4 (3; 6.75)	4 (3; 6)	0.84
Range	2 to 21	2 to 21	2 to 21	
Total follow-up time in study (years)				
Median (IQR)	2.51	2.52	2.49	0.13
Range	0.49 to 10.5	0.49 to 10.5	0.50 to 10.2	
Follow up time for BMI eval (years)				
Median	2.0	2.0	2.0	0.30
Range	0.39 to 10.2	0.39 to 9.99	0.49 to 10.2	
Race				
Caucasian	954	446	508	0.55
African American	27	13	14	
Asian	13	7	6	
American Indian/AK native	3	1	2	
Native HI/Pac.Islander	3	3	0	
Missing/unknown	117	65	53	
Ethnicity				
Non-Hispanic	914	436	478	0.15
Hispanic	161	87	74	
Missing/unknown	42	11	31	
BMI Percentile at 1st BMI eval				
Median (IQR)	63.8 (36.6; 84.6)	63.9 (38.8; 84.6)	63.5 (34.2; 84.8)	0.76
Range	0.0 to 99.9	0.2 to 99.7	0.0 to 99.9	
BMI Category at 1st BMI eval				
Underweight	47	25	22	0.84
Normal Weight	795	378	417	
Overweight	151	74	77	
Obese	124	57	67	
Cumulative excess BMI (ceBMI)				
Median (IQR)	-1.88(-3.6; -0.04)	-1.95 (-3.5;-0.2)	-1.8 (-3.7; 0.032)	0.54
Range	-10.0 to 15.1	-9.2 to 15.1	-10.0 to 14.7	
<0	844	407	437	0.67
≥0	273	127	146	
HLA DR3/4 status				
Neither	161	80	81	0.74
DR3 and/or DR4	787	377	410	
Missing	169	77	92	
Antibody status at 1st BMI eval				
Single Ab+	367	193	174	0.03
Multiple Ab+	750	341	409	
OGTT result at 1st BMI eval				
Normal	769	371	398	0.34
Abnormal†	250	111	139	
Missing	98	52	46	

* p-values reflect differences by sex. †Abnormal OGTT defined as fasting blood glucose 100-125mg/dl and/or 2-hour glucose 140-199mg/dl.

Table 2. ceBMI increases risk of progression to type 1 diabetes

	All subjects		Male		Female	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
ceBMI	1.063(1.03- 1.10)	0.0006	1.09 (1.04 -1.15)	0.0005	1.04(0.99-1.09)	0.11
ceBMI $\geq$ 0*	*1.63 (1.22-2.18)*	*0.0009*	1.60(1.08-2.36)	0.018	1.74(1.12-2.69)	0.013

Hazard ratios corresponding 95% confidence intervals, and p-values for various multivariable models for time to type 1 diabetes by age- and sex-based groups. All models adjusted for age at first BMI evaluation, sex, and whether or not they were single versus multiple Ab+ at their first BMI evaluation, except for models that are specific to one of those groups. * ceBMI$\geq$0 represents CDC sex and age specific BMI threshold for the 85th percentile.

Table 3. Age- and sex-specific ceBMI diabetes risk thresholds

		OVERWEIGHT/OBESE THRESHOLD*			DIABETES RISK THRESHOLD†		
	Age	**ceBMI**	**HR (95% CI)**	**p value**	**ceBMI**	**HR (95% CI)**	**p value**
Overall	≥12	0	1.64(0.92-2.92)	0.095	4.6	2.92 (1.41-6.04)	0.004
	<12	0	1.68(1.2-2.35)	0.03	-1.4	1.78 (1.30-2.44)	0.0003
Male	≥12	0	1.11 (0.50-2.45)	0.79	5	3.62 (1.38-9.52)	0.009
	<12	0	1.85 (1.17-2.90)	0.008	2.5	2.83 (1.58-5.08)	0.0005
Female	≥12	0	2.91 (1.15-7.39)	0.024	0	2.91 (1.15-7.39)	0.024
	<12	0	1.54 (0.93-2.57)	0.095	-1.35	1.70 (1.09-2.66)	0.02

Hazard ratios corresponding 95% confidence intervals, and p-values for various multivariable models for time to type 1 diabetes by age- and sex-based group using age- and sex-specific ceBMI cut-points. All models adjusted for age at first BMI evaluation, sex, and whether or not they were single versus multiple Ab+ at their first BMI evaluation, except for models that are specific to one of those groups. * ceBMI≥0 represents CDC sex and age specific BMI threshold for the 85th percentile. † ceBMI ≥ values identified by recursive partitioning within particular strata to give group-specific diabetes risk thresholds